Novel Oxidative Photochemical Aporphine Synthesis. Total Synthesis of Corunnine and Nandazurine

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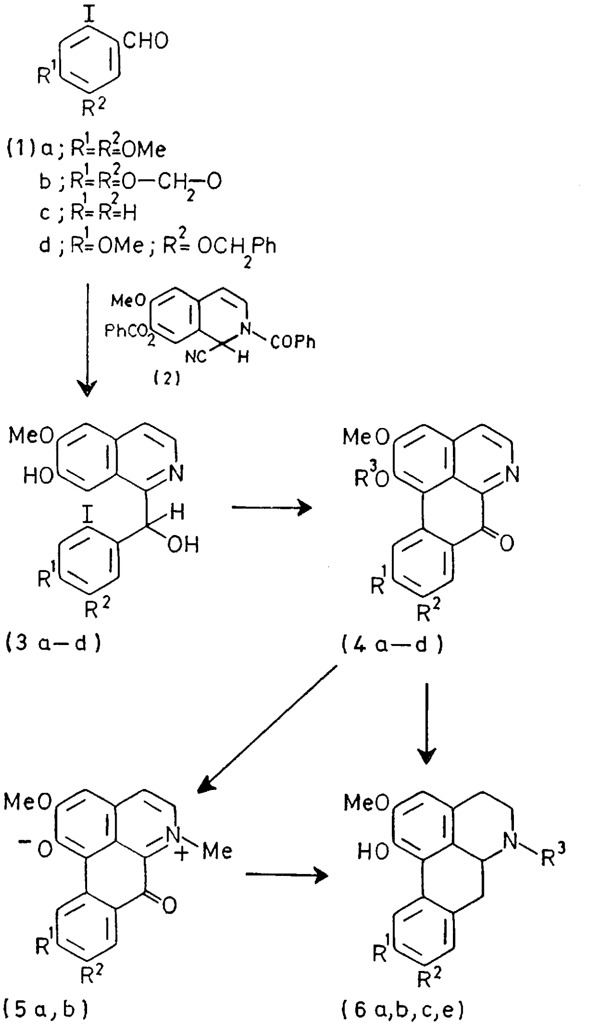
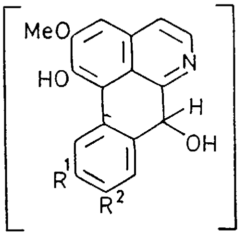
Summary A novel and efficient synthesis of aporphines, *via* oxidative photocyclisation of 1-(α-hydroxy-2-iodobenzyl)-7-hydroxyisoquinolines to phenolic 7-oxoaporphines, has been developed.

APORPHINES, which contain the tetracyclic skeleton shown in structure (**6**), have been investigated for many years.[1] Nevertheless, with few exceptions,[2-6] cyclisations to aporphine derivatives have been inefficient or limited in applicability. We describe here a novel oxidative photochemical synthesis of the aporphine ring system, and its application to the efficient synthesis of the alkaloids (±)-caaverine (**6c**; $R^3 = H$) and (±)-isoboldine (**6e**; $R^1 = OMe$, $R^2 = OH$, $R^3 = Me$). The unambiguous direct syntheses of the novel zwitterionic oxoaporphine alkaloids corunnine (**5a**)[7] and nandazurine (**5b**)[8] are also reported.

The key step in our synthesis is the oxidative photocyclisation of isoquinolines (**3a**—**d**),† readily available from condensation[9] of the appropriate *o*-iodobenzaldehydes (**1a**—**d**) with the Reissert compound (**2**) in the presence of NaH in DMF. Photolyses were carried out, as described earlier,[10] on solutions of (**3a**—**d**) in methanol at or near neutrality, to yield highly insoluble products. The products were purified and characterised by acetylation to the *O*-acetates (**4a**, **b**, and **d**; R^3 = MeCO) or conversion into the crystalline trifluoroacetate of (**4c**; R^3 = H). We attribute the exceptionally high yields of photolysis products (71—79%) chiefly to the marked insolubility of the photocyclisation products under the reaction conditions, and to their consequent removal from the photolysis medium before being subjected to further photochemical transformation. The expected products (**7a**—**d**) are probably transients in these reactions, and suffer immediate oxidation to the fully conjugated planar products (**4a**—**d**).





(7a—d)

The versatility of the oxoaporphine derivatives (**4a**—**d**) as aporphine alkaloid precursors was demonstrated by the synthesis of several target alkaloids. Hydrolysis of (**4a**) followed by *N*-methylation yielded corunnine[7] (**5a**; 69%) and corresponding treatment of (**4b**) gave nandazurine[8] (**5b**; 73%). Reduction of (**5a**) with Zn–AcOH gave (±)-thalicmidine[4] (**6a**; R^3 = Me; 63%) and similar reduction of (**5b**) gave (±)-domesticine[5] (**6b**; R^3 = Me, 75%). When (**4c**) was reduced with Zn–AcOH and the crude product treated with HBr, (±)-caaverine hydrobromide (**6c**; R^3 = H; 72%) was obtained. Hydrolysis of (**4d**) followed by catalytic reduction and *in situ* methylation with formaldehyde (Pt; 5% Pd/C, HOAc) afforded (±)-isoboldine (**6e**; R^1 = OMe, R^2 = OH, R^3 = Me) isolated as the hydrochloride (50%). Liberation of the free base gave crystalline (±)-isoboldine (**6e**; R^1 = OMe, R^2 = OH, R^3 = Me, m.p. 207—208°).

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† All new compounds have been characterised by concordant analytical and spectral data.

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